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| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |

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| 1635 | |

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/781,356 | FAN, JIAN-QIANG | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6,11-13,21,26-28,33 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,14-20,22-25,29-32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/17/04; 11/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Claims 1-8, 10, 14-23, 25, 26, 29-35, 37, and 38 generic to a plurality of disclosed patentably distinct species of active site-specific chaperones comprising 1-deoxygalactonojirimycin, alpha-allo-homonojirimycin, alpha-galacto-homonojirimycin, alpha-1-C-butyl-deoxynojirimycin, calystegine $A_3$, calystegine $B_2$, N-methyl-calystegine $A_3$, and N-methyl-calystegine $B_2$, isofagomine, N-dodecyl-isofagomine, N-nonyl-isofagomine, N-dodecyl-deoxynojirimycin, calystegine $B_3$ and calystegine $C_1$, as well as structures set forth in claim 7 wherein $R_0$ represents H or a $C_1$-$C_{12}$ alkyl chain; $R_1$ and $R_1$' independently represent H, OH, a 1-4 carbon alkyl alkoxy or hydroxyalkyl group; $R_2$ and $R_2$' independently represent H, OH or a $C_1$-$C_{12}$ alkyl group $R_4$ and $R_4$' independently represent H, OH; and $R_7$ represents H or OH, and the structures set forth in claim 10 wherein $R_0$ represents H or a $C_1$-$C_{12}$ alkyl chain; $R_0$' represents H, a straight chain or branched saturated carbon chain containing 1-12 carbon atoms, optionally substituted with a phenyl, hydroxyl or cyclohexyl group; $R_1$ and $R_1$' independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group; and $R_2$ and $R_2$' independently represent H, OH or a $C_1$-$C_{12}$ alkyl group.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, i.e. a single structure, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the

case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Stephanie Amoroso on 5/31/05 a provisional election was made with traverse to prosecute the invention of 1-deoxygalactonojirimycin, readable on claims 1-5, 7-10, 14-20, 22-25, 29-32, and 34-37. Ms. Amoroso informed the Examiner that 1-deoxygalactonojirimycin was not an active site-specific chaperone for beta-glucocerebrosidase, and so did not read on claims limited to active site specific chaperones from this protein (i.e. claims 6, 21, and 33). Affirmation of this election must be made by Applicant in replying to this Office action. Claims 6, 11-13, 21, 26-28, 33, and 38-40 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claims 1-5, 7-10, 14-20, 22-25, 29-32, and 34-37 and the species of 1-deoxygalactonojirimycin are under consideration in this Office Action.

***Specification***

At page 5, line 17, Applicant incorporates by reference application No. 10/304,396. However, this Application is unrelated to the instant application and has recently issued as US Patent No 6,863,665, "Disposable Waste Containment Garment". Deletion of this reference is required.

### *Drawings*

The Application as filed contained no drawings.

### *Claim Objections*

Claim 6 is objected to because it as two periods.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 29-32 and 34-37 arerejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 29-32, and 34-37 are indefinite because claims 4 and 30 recite "the enzyme" without antecedent basis.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Written Description*

Claims 29-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 29-32, and 34-37 are drawn to methods of treating individuals having a disorder from the genus of disorders "requiring gene therapy." The limitation "a disorder requiring gene therapy" is interpreted to mean that the disorder cannot be treated without gene therapy, or that gene therapy is the clear treatment of choice. The specification fails to describe any disorder that requires gene therapy, i.e. that is treatable only by gene therapy or in which gene therapy is the clear treatment of choice. This disclosure does not convey to one of skill in the art that Applicant was in possession of the claimed genus of methods at the time the invention was filed.

***Enablement***

Claims 1-5, 7-10, 14-20, 22-25, 29-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of gene therapy for disorders caused by a deficiency in a protein comprising administering to an individual an expression vector encoding the protein, the improvement comprising administering an active site specific chaperone of the protein wherein the active site specific chaperone stabilizes a functional conformation of the protein, does not reasonably provide enablement for methods of treating an individual having a disorder requiring gene therapy, or methods of increasing the expression level of polypeptides in vivo, as broadly claimed. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

*Nature of the Invention and Breadth of the Claims*

Claims 1-5, 7-10, 14-20, and 22-25 are directed to methods of increasing the level of expression of a recombinant protein in vivo in cells of an individual wherein the protein is expressed from an expression vector that has been introduced into the cells, wherein the method comprises administering to the individual an active site-specific chaperone of the protein. The specification is directed generally to methods of augmenting gene therapy, and contemplates no purpose for increasing the level of expression of any protein in vivo other than therapy. As a result claims 1-5, 7-10, 14-20, and 22-25 are reasonably interpreted as methods of gene therapy. Claims 29-32 and 34-37 are directed to methods of treating an individual having a disorder requiring gene therapy, comprising administering to the individual a composition comprising a therapeutic vector encoding a protein and an active site-specific chaperone for the protein.

The specification generally discloses the invention as a means to improve the efficiency of gene therapy for protein deficiencies by combining standard gene therapy approaches with an active site-specific chaperone (ASSC), i.e., an agent capable of inducing the proper/native folding conformation of the protein, and stabilizing the protein encoded by the gene. See page 7, lines 24-27. More specifically, the specification discloses the invention as a means of treating an individual suffering from a disorder that is treatable by gene therapy (page 7, lines 5-8). However, the specification also

discloses the invention as a method of generally improving the expression, stability, and activity of proteins in cells (see page 7, lines 9-18), and contemplates therapy of diseases that are not currently treatable by gene therapy, such as cystic fibrosis. So, the claims can be reasonably interpreted as embracing new methods of gene therapy that are made possible by the asserted improvements in protein expression, stability, and activity acquired through addition of an ASSC. In brief, the specification is considered to be enabling for improving existing gene therapy methods, but does not enable gene therapies that otherwise lacked enablement at the time of the invention.

*Gene Therapy, State and Predictability of the Art*

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story" (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Central to the problem of sustained expression is a difficulty in obtaining sufficient transcription of therapeutic genes. See page 240, column 2, lines 10-17, column 2, line 36 to column 3, line 1, and column 3, lines 20-23. Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered." Anderson indicates that the reason for poor

expression is a lack of understanding as to how vectors should be constructed, particularly with regard to what regulatory sequences (i.e. transcription control sequences) are appropriate. See page 30, fourth full paragraph. More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector, including the ability to support sustained and regulated expression. See page 91, column 1, lines 5-13 of first paragraph. At the time the invention was filed, there were scattered successes in the field of in vivo gene delivery and expression. For example, Yew et al (US Patent 6,066,626) taught methods for providing a biologically active alpha galactosidase to cells of an individual having a deficiency of that enzyme by administration into cells of the individual an expression construct encoding alpha galactosidase.

However, the instant specification contemplates gene therapy of other diseases with a high level of unpredictability in view of the state of the art and the teachings of the specification. For example, at page 14, line 26, and at Table 2 on page 20, the specification identifies cystic fibrosis (CF) as a disease treatable by gene therapy. The state of the art of CF gene therapy at the time of the invention is set forth by several

authors. The example of CF shows why gene therapy must be tailored to fit specific diseases on a case by case basis, and why no single gene therapy method will be effective to treat all diseases. For example, one of the most important barriers to gene therapy of CF is the lack of information regarding the appropriate target cells for gene delivery. Rosenfeld and Collins (Chest 109:241-252, 1996) taught that it is unclear exactly which cells should receive gene therapy, stating that "[t]he difficulty in determining which cells to target relates to an inability to draw parallels between the normal pattern of CFTR expression and the development of CF in lung disease. See also Ferrari et al (Adv. Drug Del. Rev 54:1373-1393, 2002), especially section 7 at pages 1384-1385. In normal individuals, the surface epithelium of small airways expresses very low levels of CFTR, while the submucosal glands found exclusively in large airways express much higher levels. In contrast, in CF, the most important pathologic consequences occur first in the small airways with alveolar damage as a consequence. Little if any clinically significant disease ever occurs where the submucosal glands are found." Boucher (TIG 12(3): 81-84, 1996) noted that this issue is relevant to strategies for vector delivery because while the superficial epithelium of airways can be reached by lumenal vector delivery, the submucosal glands may require systemic administration. See page 1 of reprint, column 2, last sentence of first full paragraph. Rosenecker (Eur. J. Med. 23(3): 149-156, 3/1998) taught that "[t]opical administration of gene transfer vectors to airways is impeded by surface fluid, mucus plugging the airway lumen, and the ciliated apical surface of epithelial cells" and that the submucosal glands are inaccessible for topically applied formulations. Thus systemic

delivery via the blood stream is indicated. See page 152, column 2, lines 1-15 of second full paragraph. Thus, at the time of the invention and afterwards, those of skill in the art were uncertain as to which cells should be considered targets for CF gene therapy, and what route of delivery would lead to success, assuming the art-recognized problems relating to gene expression after delivery could be solved.

The situation in CF gene therapy is further complicated by an incomplete understanding of the pathophysiology of the disease. Briefly, the molecular problem responsible for CF is a defect in a chloride ion transporter known as CFTR. One hypothetical explanation for the progress of the disease depends on a failure to transport chloride ions, leading to abnormal absorption of sodium ions by the epithelium. This leads to dehydration and thickening of the mucus in the lungs, which in turn leads to a variety of pathophysiological outcomes including inflammation, repeated infections, and decreasing pulmonary function. Alternatively, the defect in CFTR could somehow affect the actual composition of mucus in the lung, resulting in the recognized pathologies. See Wilson (1995) paragraph bridging pages 2547 and 2548. Thus a primary focus of treatment is the restoration of chloride ion transport. Boucher (1999) taught that it is likely that the percentage of epithelial cells requiring functional correction to restore normal chloride ion transfer *in vivo* may well exceed 10%, and advises that the simplest strategy to assure efficacy is to mimic the normal pattern of *in vivo* expression by achieving gene expression in 100% of lung epithelial cells. See paragraph bridging pages 441 and 442, page 442 column 1, lines 25-30, and 42- 45. See also Ferrari et al (Adv. Drug Del. Rev 54:1373-1393, 2002), especially section 7 at

pages 1384-1385. Boucher concluded that a one or two order of magnitude increase in *in vivo* gene transfer efficiency, above that observed in clinical trials, will be required for therapeutic relevance in CF treatment. See page 444, column 2, first sentence of second full paragraph. The state of the art at the time of the invention provided insufficient means to achieve this level of delivery and expression (see Verma (1997), Anderson (1998), Somia (2000) and Romano (2000), above), and Ferrari et al (2002) indicated that delivery and expression were still primary barriers to CF gene therapy after the time of the invention. See abstract. Clinical studies have shown success in partially correcting chloride ion transport, however Alton and Geddes (1997) taught that it is unknown whether the chloride or sodium defect associated with CF is the more important error to correct, and that the degree of correction needed for clinical benefit of these defects is unknown. See page 45, lines 7-10 of first full paragraph. Furthermore, Davies (1998) taught that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Rosenfeld (1996) indicates that although restoration of chloride conductance in monolayer cells is achieved by transfection of 5-7% of the cells, normalization of sodium ion reabsorption will require transfection of a much higher percentage of cells. See page 243, column 1, lines 15-18. After the time of filing, Ferrari et al (2002) found that although some progress had been made in overcoming the barriers to gene therapy of CF, treatment was still not feasible because "current levels of gene transfer efficiency are probably to

low". See abstract, and Fig. 1 on page 1376 for a summary of the barriers to gene delivery in cystic fibrosis. For all these reasons it was apparent at the time of the invention that the practice of gene therapy of CF was highly unpredictable, and that the state of the art could not support gene therapy of CF.

*Active Site-Specific Chaperones, State of the Art*

At the time the invention was filed it had been shown that active site-specific chaperones could be used to induce improved folding of mutant enzymes that otherwise lacked the capacity to fold properly (see e.g. Fan (Trends in Pharm. Sci. 24(7): 355-360, 2003)). The essence of the idea is that certain mutations lead to improper folding of enzymes, but do not necessarily eliminate enzyme activity. The improperly folded mutant enzymes are retained in the endoplasmic reticulum and then degraded resulting in a deficiency of the enzyme. Addition of an active site-specific chaperone promotes proper folding of the mutant enzymes and can lead to production of catalytically active enzymes if the mutation does not otherwise interfere with enzyme structure and mechanism. See e.g. abstract, paragraph bridging pages 355 and 356. In this way active site-specific chaperones can be used to increase the level of expression of potentially active enzymes that would otherwise be misfolded and degraded.

A variety of ASSCs was known in the prior art. The specification and prior art taught that a variety of alpha galactosidase inhibitors could be used to promote proper folding of alpha galactosidase in vivo. See e.g. Fan et al, US Patent 6,274,597, claims 1 and 5). Fan et al (US Patent 6,589,964) disclosed a variety of imino sugars and methods of using them to enhance the activity of a variety of lysosomal enzymes

involved in lipid storage diseases. See claims. The specification discloses by reference to non-patent publications ASSCs for p53, vasopressin receptor, human opioid receptor, HERG (a rectifying $K^+$ channel), P-glycoprotein (multidrug resistance), CFTR, and rhodopsin. See e.g. page 27, line 27 to page 28, line 14.

*Guidance and Examples in the Specification*

The specification provides no guidance as to how to overcome art recognized barriers to gene therapy such as poor gene delivery and inadequate transcription, beyond that which was known in the prior art. Guidance relevant to these problems is given at pages 21-26, and is limited to a review of prior art methods.

*Amount of Experimentation Required*

As discussed above, the state of the art of gene therapy at the time of the invention was such that one of skill in the art could not routinely obtain success in general, due to deficiencies in gene delivery and expression. Due to the complexities of diseases, enablement of gene therapies must be considered on a disease by disease basis, as is evident from the review of CF gene therapy, above. Absent specific guidance as to how to overcome the art-recognized barriers to gene therapy of poor gene delivery and expression, and absent guidance specific to each disease to be treated, one of skill in the art would have to perform undue experimentation in order to use the claimed invention to treat diseases for which gene therapies did not already exist at the time of the invention. This rejection can be overcome by limiting the claims to methods of improving gene therapies, as suggested in the statement of the rejection above.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with Fan et al (US Patent 6,274,597.

Yew taught methods of providing biologically active human alpha galactosidase-A to cells of an individual having a deficiency of that enzyme (Fabry's disease) by administration into cells of the individual an adenoviral expression construct encoding alpha galactosidase. See claim 8. The cells may be in vivo (see claims) or ex vivo (see column 9, lines 10-14).

Yew did not teach an active site-specific chaperone.

Fan '597 taught methods of increasing the activity of a mutant form of lysosomal alpha galactosidase-A in mammalian cells, and treating Fabry's disease in an individual, comprising administering an effective amount of 1-deoxygalactonojirimycin. See claims 1-7.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat an individual with Fabry's disease by administering both the expression construct of Yew, and 1-deoxygalactonojirimycin. One would have been motivated to augment the method of Yew by combining it with the method of Fan above

because, in addition to providing the wild type protein of Yew, one would have expected to obtain activity from the patient's endogenous mutant protein as a result of the method of Fan, thereby providing more alpha galactosidase-A activity than would have been obtainable by the separate methods.

Thus the invention as a whole was prima facie obvious.

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with and any one of Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), or Fan et al (US Patent 6,774,135, issued 8/10/2004).

The applied references Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), and Fan et al (US Patent 6,774,135, issued 8/10/2004) have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, they constitute prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior

inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Yew taught methods of providing biologically active human alpha galactosidase-A to cells of an individual having a deficiency of that enzyme (Fabry's disease) by administration into cells of the individual an adenoviral expression construct encoding alpha galactosidase. See claim 8. The cells may be in vivo (see claims) or ex vivo (see column 9, lines 10-14).

Yew did not teach an active site-specific chaperone.

Fan '964 taught methods of increasing the activity of a mutant form of lysosomal alpha galactosidase-A in mammalian cells, and treating Fabry's disease in an individual, comprising administering an effective amount of 1-deoxygalactonojirimycin. See e.g. claims 1-10, and 41-47, especially claims 9, 10 and 47.

Fan '919 taught methods of enhancing in a mammalian cell the activity of an enzyme, which enzyme when mutated tends to fold in an incorrect conformation in endoplasmic reticulum (ER), and whereby a level of the active enzyme is deficient as a result of such mutation, which method comprises administering a competitive inhibitor of the enzyme in an amount effective to enhance enzyme activity, wherein said competitive inhibitor is 1-deoxygalactonojirimycin. See claims 1-16, and 18-42, especially claims 18 and 19.

Fan '135 taught methods of treating Fabry's disease comprising administering to an individual in need thereof an effective amount of 1-deoxygalactonojirimycin. See claims 1, 3, 4, 7, 9, 10, 12, 13, 15-17, 21, 23-25, 29, and 31-36.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat an individual with Fabry's disease by administering both the expression construct of Yew, and 1-deoxygalactonojirimycin. One would have been motivated to augment the method of Yew by combining with any of the methods of Fan above because, in addition to providing the wild type protein of Yew, one would have expected to obtain activity from the patient's endogenous mutant protein as a result of the methods of Fan, thereby providing more alpha galactosidase-A activity than would have been obtainable by the separate methods.

Thus the invention as a whole was prima facie obvious.

Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with Fan et al (US Patent 6,274,597) as applied to claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 above, and further in view of Hendricks et al (Blood 96 (11 part 1): 845a, 2000).

The teachings of Yew and Fan are discussed above, and can be combined to render obvious methods of increasing the level of expression of alpha galactosidase in an individual by administering to the individual cells comprising an alpha galactosidase expression vector and 1-deoxygalactonojirimycin.

Yew and Fan did not teach administration of human primary cells or mesenchymal stem cells comprising an alpha galactosidase expression vector.

Hendricks taught a method in which human mesenchymal stem cells were transduced with a retroviral expression vector encoding alpha galactosidase A, and then were implanted into mice where they secreted high levels of alpha galactosidase A suggesting their usefulness as gene delivery vehicles for the treatment of Fabry's disease. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer human mesenchymal stem cells comprising an alpha galactosidase A expression vector to a human individual for the purpose of increasing the expression level of alpha galactosidase A in the individual. One would have been motivated to do so because Hendricks suggests that human mesenchymal stem cells transduced to express alpha galactosidase A would be useful as gene delivery vehicles for the treatment of Fabry's disease.

Thus the invention as a whole was prima facie obvious.

Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with any one of Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), or Fan et al (US Patent 6,774,135, issued 8/10/2004) as applied to claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 above, and further in view of Hendricks et al (Blood 96 (11 part 1): 845a, 2000).

The teachings of Yew and Fan '964, '919, and '135 are discussed above and can be combined to render obvious methods of increasing the level of expression of alpha galactosidase in an individual by administering to the individual cells comprising an alpha galactosidase expression vector and 1-deoxygalactonojirimycin.

Yew and Fan did not teach administration of human primary cells or mesenchymal stem cells comprising an alpha galactosidase expression vector.

Hendricks taught a method in which human mesenchymal stem cells were transduced with a retroviral expression vector encoding alpha galactosidase A, and then were implanted into mice where they secreted high levels of alpha galactosidase A suggesting their usefulness as gene delivery vehicles for the treatment of Fabry's disease.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer human mesenchymal stem cells comprising an alpha galactosidase A expression vector to a human individual for the purpose of increasing the expression level of alpha galactosidase A in the individual. One would have been motivated to do so because Hendricks suggests that human mesenchymal stem cells transduced to express alpha galactosidase A would be useful as gene delivery vehicles for the treatment of Fabry's disease.

Thus the invention as a whole was prima facie obvious.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,274,597 in view of Yew et al (US Patent 6,066,626).

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, and 41-47 of U.S. Patent No. 6,589,964 in view of Yew et al (US Patent 6,066,626).

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16, and 18-42 of U.S. Patent No. 6,599,919 in view of Yew et al (US Patent 6,066,626).

Claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1, 3, 4, 7, 9, 10, 12, 13, 15-17, 21, 23-25, 29, and 31-36 of U.S. Patent No. 6,774,135 in view of Yew et al (US Patent 6,066,626).

The combination with Yew of each of the '597, '964, '919, and '135 patents is discussed above under 35 USC 103 rejections. The claims of each of these patents as listed above embrace methods of administering 1-deoxygalactonojirimycin to humans for the purpose of increasing the expression or activity of alpha galactosidase in Fabry's disease.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat an individual with Fabry's disease by administering both the expression construct of Yew, and 1-deoxygalactonojirimycin. One would have been motivated to augment the method of Yew by combining with any of the methods of '597, '964, '919, or '135 because, in addition to providing the wild type protein of Yew, one would have expected to obtain activity from the patient's endogenous mutant protein as a result of the methods of '597, '964, '919, or '135, thereby providing more alpha galactosidase-A activity than would have been obtainable by the separate methods.

Claims 18 and 19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of the '597, '964, '919, or '135 patents cited above and Yew et al (US Patent 6,066,626) as applied to instant claims 1-5, 7-10, 14-17, 19, 20, 22-25, 29-32, and 34-37 above, and further in view of Hendricks et al (Blood 96 (11 part 1): 845a, 2000).

The teachings of Yew and Fan '597, '964, '919, and '135 are discussed above and can be combined to render obvious methods of increasing the level of expression of alpha galactosidase in an individual by administering to the individual cells comprising an alpha galactosidase expression vector and 1-deoxygalactonojirimycin.

Yew and Fan did not teach administration of human primary cells or mesenchymal stem cells comprising an alpha galactosidase expression vector.

Hendricks taught a method in which human mesenchymal stem cells were transduced with a retroviral expression vector encoding alpha galactosidase A, and then were implanted into mice where they secreted high levels of alpha galactosidase A suggesting their usefulness as gene delivery vehicles for the treatment of Fabry's disease.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer human mesenchymal stem cells comprising an alpha galactosidase A expression vector to a human individual for the purpose of increasing the expression level of alpha galactosidase A in the individual. One would have been motivated to do so because Hendricks suggests that human mesenchymal stem cells transduced to express alpha galactosidase A would be useful as gene delivery vehicles for the treatment of Fabry's disease.

Thus the invention as a whole was prima facie obvious.

## ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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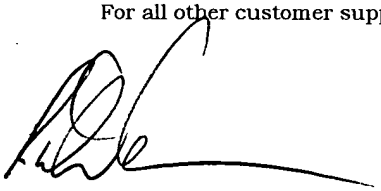

Richard Schnizer, Ph.D.